DEPARTMENT OF HEALTH AND HUMAN SERVICES

Reference Numbers: 95-0001 and 95-0022 MAR 29 1996

Barry Garfinkle, Ph.D.
Merck and Company, Inc.
Sumneytown Pike
West Point, PA 19486

Dear Dr. Garfinkle:

Enclosed is a product license authorizing Merck and Company, Inc., U.S. License No. 2, to manufacture and ship Hepatitis A Vaccine, Inactivated, in the United States for sale, barter, or exchange.

Under this license you are authorized to manufacture and prepare for sale, Hepatitis A Vaccine, Inactivated, for the immunization of persons two years of age and older. This license will permit you to export bulk to be filled at your contract facility at [redacted] and import filled syringes to be prepared for sale in the United States. The vaccine will be presented in 25 U/0.5mL single dose vials and prefilled syringes for the immunization of children and 50 U/1.0mL single dose vials and prefilled syringes for adult immunization. We acknowledge the manufacturing scheme set forth in your submission of January 3, 1996.

You are requested to submit for testing a sample of the bulk and samples of product in final containers together with protocols showing results of all applicable tests. No lots of product shall be distributed until notification of release is received from the Director, Center for Biologics Evaluation and Research.

The dating period for this product shall be 18 months from the date of manufacture when stored at 2-8° C. The date of manufacture shall be defined as the date of the last valid potency test performed on final container material. Prior to final container filling, bulk material may be stored for 33 months at 2-8° C, including not more than 3 months of storage at the diluted bulk stage. These dating and storage periods are contingent upon your commitment to conduct ongoing stability studies of your launch lots as outlined in your letter of March 29, 1996, and to withdraw from the market any lots which fall out of specifications during the expiration dating period.

Changes in the manufacture, testing, packaging or labeling of Hepatitis A Vaccine, Inactivated, or in the manufacturing facilities may require the submission of a Supplement to either your Product or Establishment License Application for our review and written approval prior to implementation.

We acknowledge the following commitments made in your letters dated March 21 and 26, 1996,

1. to submit a protocol, and discuss with CBER, a suitable postmarketing safety trial to assess the incidence of rare or unusual adverse events,

2. to submit for review by CBER, within three months of the date of this letter, a protocol describing studies to evaluate the concomitant administration of VAQTA and other travelers' vaccines, and

3. to submit for review by CBER a Supplement to your Product License Application to describe the the addition of a midpoint filtration during the hepatitis A inactivation process; this filtration was implemented beginning with sequential lot number 133.

These commitments have been made a part of your Product License Application for this product.

If you wish to request extention of the dating period for this product or storage period for the bulk you may do so by submitting a Supplement to your Product License Application along with documentation supporting the real-time stability of the product or bulk.

It is requested that adverse experience reports for Hepatitis A Vaccine, Inactivated, be submitted in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and that distribution reports be submitted as described (21 CFR 600.81). Since your product is categorized as a vaccine, these reports should be submitted to the Vaccine Adverse Event Reporting System (VAERS) using the pre-addressed form VAERS-1.

Please submit three copies of final printed labeling at the time of use and include part II of the label transmittal form with completed implementation information. In addition, please submit three copies of the introductory advertising and promotional labeling. You may wish to submit the proposed materials in draft form with an FDA form 2567 to the Center for Biologics Evaluation and Research, Advertising and Promotional Labeling Staff, HFM-202, 1401 Rockville Pike, Rockville, MD 20852-1448. Promotional claims should be consistent with and not contrary to approved labeling. No comparative claims or claim of superiority over other similar products should be made unless data to support such claims are submitted to and approved by the Center for Biologics Evaluation and Research.

Please acknowledge receipt of the enclosed product license to the Director, Division of Vaccines and Related Products Applications, HFM-475, Center for Biologics Evaluation and Research.

Also, your request to supplement your Establishment License Application to provide for the manufacture of Hepatitis A Vaccine, Inactivated, at your West Point, PA facility has been approved.

Establishment License Number 2, is hereby reissued to Merck and Company, Inc., West Point, PA, with the designation of two locations effective this date. Hepatitis A Vaccine, Inactivated, will be manufactured, formulated and filled into vials at your West Point, PA location and formulated and filled into syringes at the [redacted] location. This license authorizes you to manufacture and ship for sale, barter, or exchange those products for which your establishment holds an unsuspended and unrevoked product license issued by the U.S. Department of Health and Human Services.

Establishment License Number 2, dated March 16, 1995, should be forwarded to the Director, Division of Establishment Licensing (HFM-205), Center for Biologics Evaluation and Research. This license should be returned in order that notation of the revocation may be made thereon, after which it may be returned to you for your files.

We acknowledge the following commitments made in your letters dated January 30 and March 20, 1996:

1. to evaluate the downstream manufacturing process, including final filtration step, using media challenge and to provide a protocol summary and data by April 30, 1996,

2. to evaluate aseptic manipulations associated with the bioreactors and to provide a protocol summary and data by June 30, 1996, and

3. to provide cleaning validation summaries for product contact equipment used on filling line — by May 15, 1996.

The information contained in the above referenced supplement will be included in your Establishment License Application file.

Sincerely yours,

M. Carolyn Hardegree, M.D.
Director
Office of Vaccines
Research and Review
Center for Biologics
Evaluation and Research

Jerome A. Donlon, M.D., Ph.D.
Director
Office of Establishment
Licensing and Product Surveillance
Center for Biologics
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